**REMARKS**

Claim 61 is pending in the subject application. By this Amendment, applicants have amended claim 61, the sole claim pending in the application.

Applicants note that the amendments to claim 61 are merely formatting changes which serve to delete a superfluous word ("the") and phrase ("or a macrophage-tropic HIV-1-infected cell") from the claim. Applicants note that this phrase is a carry-over from a previous version of claim 61 and its recitation is unnecessary for the invention now claimed. Applicants maintain that these amendments to claim 61 raise no issue of new matter. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claim 61, as amended, will be pending and under examination.

Applicants again thank the Examiner for the courtesy extended during the interview held on December 7, 2004, a Summary of which was prepared by the Examiner on December 7, 2004 and a Communication regarding which was filed by applicants on January 4, 2005.

**The Invention**

The invention claimed in the subject application provides a method of inhibiting infection of a CD4+ cell by a macrophage-tropic HIV-1. This method comprises contacting the CD4+ cell with an agent which is capable of binding to a CCR5 chemokine receptor on the surface of the CD4+ cell and blocking fusion of HIV-$1_{JR-FL}$ with a PM-1 cell, but is not capable of blocking fusion

of HIV-$1_{BRU}$ with such PM-1 cell. The agent is administered in an amount and under conditions such that fusion of the macrophage-tropic HIV-1 to the CD4+ cell is inhibited, so as to thereby inhibit infection of the CD4+ cell by the macrophage-tropic HIV-1.

**Rejection under 35 U.S.C. §112, First Paragraph**

Written Description

The Examiner rejected claim 61 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention (citing *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981); *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90. (C.C.P.A. 1976)). The Examiner stated that the claim is directed toward a method of inhibiting HIV-1 macrophage-tropic infection of a $CD4^+$ cell by contacting said cell with an agent that is capable of binding to cell surface CCR5. The Examiner further stated that the claim also stipulates that said agent blocks HIV-$1_{JR-FL}$ fusion with a PM-1 cell while not affecting fusion of HIV-$1_{BRU}$ with the same cell type.

The Examiner noted that, as previously set forth, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (citing, e.g., *Vas-Cath, Inc., v. Mahurkar,* 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116. The Examiner also stated that the issue raised in this application is whether the original application provides adequate support

for the broadly claimed genus of agents that are capable of abrogating HIV-1 infection by binding to the CCR5 chemokine receptor. The Examiner further stated that an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention (citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997)).

In addition, the Examiner stated that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making, coupled with its function, and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. The Examiner stated that a biomolecule sequence, described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest (citing *In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993); *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995)).

The Examiner stated that a lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process (citing, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995)). The Examiner further stated that the court noted in this decision that a "laundry list" disclosure of

every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

The Examiner also stated that an applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. The Examiner further stated that an applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. The Examiner additionally stated that for some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight.

The Examiner stated that the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. The Examiner further stated that without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely. The Examiner also stated that in the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement (citing *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43

U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998); *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984)). The Examiner noted that factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

In response, applicants respectfully traverse this "written description" rejection for the reasons set forth below. Applicants assert that, contrary to the focus of the Examiner's rejection, the pending claim is not directed to an agent but instead is directed to a method of inhibiting infection of a CD4+ cell by a macrophage-tropic HIV-1 strain. Nevertheless, applicants address below the points raised by the Examiner regarding the agent used in the method recited in claim 61.

Applicants reiterate the Examiner's statements that factors to be considered in determining the adequacy of the written description include (1) the level of skill and knowledge in the art; and (2) disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, including, *inter alia*, (a) the method of making the claimed invention, (b) binding specificity, and (c) functional characteristics alone or coupled with a known or disclosed correlation between function and structure. With regard to the first of these factors, applicants note that the level of skill in the biotechnology arts is very high. See, for example, *Enzo Biochem, Inc. v. Calgene, Inc.* 188 F.3d 1362, (Fed. Cir. 1999):

> [T]he district court determined that a person of ordinary skill in the art would be 'a junior faculty member with one or two years of relevant experience or a postdoctoral student with several years of experience,' *see Enzo,* 14 F.Supp.2d at 567, and we discern no clear error in this determination.

This is consistent with Dr. Dragic's characterization, in her expert declaration submitted with applicants' April 2, 2002 Amendment (the "First Declaration"), of the level of skill in the art of utilizing RET assays for determining the existence of cell fusion between a CD4+ cell and an HIV-1 infected cell. Dr. Dragic stated in paragraph 8 of the First Declaration that one of ordinary skill in this art has "a Master's Degree or higher in cell biology or a related field and at least one year of experience."

As noted by the Examiner, an issue of lack of adequate written description arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosures. However, applicants contend that in an art characterized by high skill, the level of disclosure required to satisfy the written description requirements is less that would be required if the level of skill in the art was low. In support of this position, applicants respectfully direct the Examiner's attention to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, Federal Register Vol. 66, No. 4, p. 1105, Section IIA(2), which states that "[g]enerally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement." Applicants assert that in the instant case, the high level of skill in the art is a favorable factor in

assessing the sufficiency of the written description, and maintain that the claimed invention is adequately described in the specification.

Second, regarding the disclosure of relevant identifying characteristics which demonstrate their possession of the claimed invention, applicants note that the specification discloses a method (the RET assay) for identifying agents with the properties specified in the claims. In addition, applicants assert that the binding specificity of the agent and its capability, as recited in the pending claim, to inhibit fusion of a PM-1 target cell to one strain of HIV-1 ($HIV\text{-}1_{JR\text{-}FL}$) but not to another ($HIV\text{-}1_{BRU}$), are identifying characteristics of the agent disclosed in the specification. Applicants further assert that the capability of the agent to bind to a CCR5 receptor on the surface of the target cell is a function of the agent. Moreover, applicants assert that there is clearly a correlation between the function and the identifying characteristics of the agent. Accordingly, applicants maintain that the written description is adequate to show that applicants were in possession of the claimed invention. Applicants further note that, as discussed below, the specification provides working examples of β-chemokine agents which satisfy the requirements recited in the pending claim.

The Examiner stated that the claim of the instant application is broadly directed toward any agent that is capable of abrogating HIV-1 infection through CCR5 binding interactions. The Examiner also stated that the claims do not limit the genus to any particular type of compound (i.e., peptidyl, organic, fatty acid, etc.) or any particular family of compounds (small molecular weight peptidyl inhibitors, antibody-based reagents, etc.). The Examiner

further stated that the disclosure provides a generic *in vitro* resonance energy transfer (RET) screening assay that enables the skilled artisan to detect HIV-1 fusion events but that this method by itself does not lead the skilled artisan to any particular class of compounds.

In response, applicants emphasize that, contrary to the Examiner's characterization, the claimed invention is not directed to an agent *per se* but rather is directed to a method of inhibiting HIV-1 infection of a CD4+ cell by a macrophage-tropic HIV-1. This method comprises the use of an agent which is capable of capable of blocking fusion of HIV-$1_{JR-FL}$ with a PM-1 cell, but not capable of blocking fusion of HIV-$1_{BRU}$ with such PM-1 cell.

Applicants maintain that information on a particular type or family of compound is not required because agents which satisfy the claim requirements are readily identified on the basis of results of the disclosed RET screening assay. Applicants note that the specification discloses a routine, reproducible RET assay for identifying agents which exhibit the claimed characteristics. In addition, applicants note that the specification discloses examples of β-chemokines (see, *inter alia*, page 1, line 32 to page 2, line 3; page 2, lines 28-34; page 7, lines 3-30; Figure 1; page 26, lines 8-18; page 34, lines 33-37; and page 35, Table 2a) which satisfy the requirements of the pending claim. Applicants note also that the specification discloses that non-chemokine agents which inhibit fusion of HIV-$1_{JR-FL}$ with a PM-1 cell, but not fusion of HIV-$1_{BRU}$ with a PM-1 cell, may be an oligopeptide, a polypeptide, an antibody or a portion thereof, or a nonpeptidyl agent (see page 14, lines 13-22; page 20, lines 22-27). The specification

further discloses that antibodies to CCR5 which block HIV-1 infection have been demonstrated (see page 45, lines 33-35).

The Examiner also stated that the disclosure also fails to provide sufficient structural/functional guidance pertaining to suitable compounds that can reasonably be expected to function in the claimed methodology. The Examiner stated that while some data are supplied pertaining to a small number of closely related molecules (e.g., the β-chemokines), these compounds nevertheless fail to meet the basic limitations of the claim pertaining to fusion blocking activity.

In response, applicants disagree with the Examiner's position. As discussed in more detail below, applicants maintain that the β-chemokines, RANTES, MIP-1α and MIP-1β, exhibit precisely the fusion-inhibitory activities of the agent recited in claim 61.

Applicants attach hereto as **Exhibit A** a "Third Declaration Under 37 C.F.R. §1.132 of Tatjana Dragic" (the "Third Declaration"). Applicants note that this Third Declaration is being submitted following the issuance of a Final Office Action. However, applicants maintain that this Third Declaration could not have been filed earlier since it is being filed in direct response to the Examiner's objections to Dr. Dragic's two previous expert declarations, which objections were set forth for the first time in the February 9, 2005 Final Office Action. The Third Declaration also addresses the written description issues raised by the Examiner in the February 9, 2005 Final Office Action, whereas the previous declarations addressed enablement issues. Accordingly, applicants respectfully request that the Examiner enter the Third Declaration.

In her Third Declaration, Dr. Dragic reiterates that the level of skill in the art is very high, and states her expert opinion that, based on the subject application, a person skilled in the art would readily conclude that the inventors had possession of the claimed invention. Dr. Dragic predicates her opinion on the facts that (1) the specification teaches inhibition of fusion of a PM-1 cell with HIV-$1_{JR-FL}$ by agents which do not inhibit fusion of a PM-1 cell with HIV-$1_{BRU}$, and provides examples of different agents which exhibit these fusion-inhibitory properties; (2) the specification discloses identifying characteristics of the agent utilized in the claimed method, namely, its specificity in binding to the CCR5 receptor; ability to inhibit fusion of a PM-1 target cell to HIV-$1_{JR-FL}$; and inability to inhibit fusion of a PM-1 target cell to HIV-$1_{BRU}$; (3) the specification discloses a function of the agent, namely, its ability to bind to a CCR5 receptor on the surface of a target cell; (4) there is a clear correlation between this function and the identifying characteristics of the agent; and (5) the specification provides a RET assay which one skilled in the art could, as of April 2, 1996, readily use to identify additional agents that exhibit the fusion-inhibitory activities specified in the pending claims. Applicants note that these expert opinions of Dr. Dragic support their remarks presented hereinabove.

The Examiner additionally stated that the disclosure fails to provide any guidance pertaining to the molecular determinants of the CCR5 receptor that might prove to be suitable targets (i.e., epitopes, active domains, etc.). The Examiner asserted that the skilled artisan thus cannot perform a rational drug-screening approach to identify putative inhibitors. The Examiner contended that applicants have basically provided a generic screening method and invited the skilled artisan to figure out

which agents may be reasonably expected to function in the recited manner. The Examiner also stated that this clearly fails to meet the requirements set forth under this statute. The Examiner contended that the skilled artisan would accordingly reasonably conclude that applicants were not in possession of the claimed genus of compounds at the time of filing.

In response, applicants note that "rational drug design" is not the norm in the pharmaceutical industry. Applicants point out that, instead, the traditional method for identifying new candidate drugs involves screening large numbers of compounds. Applicants note that, in fact, it was only in the early 1990's that Agouron Pharmaceuticals, Inc. (now part of Pfizer, Inc.) successfully demonstrated the feasibility of rational drug design, i.e., using the detailed structure or computerized models of protein molecules to systematically synthesize drugs based on those molecular structures. Applicants note further that Agouron's first commercial drug produced by rational drug design, the HIV protease inhibitor VIRACEPT® (nelfinavir mesylate), received marketing clearance from the U.S. Food and Drug Administration only as recently as 1997. Thus, applicants maintain that rational drug design is in its infancy and that this approach to drug development is today still the exception in the pharmaceutical industry. Accordingly, applicants respectfully submit that the instant rejection of the pending claim on the ground that the specification does not permit rational drug design is entirely without merit and should be withdrawn.

Applicants also disagree with the Examiner's position that the skilled artisan is provided with a generic screening method and invited to "figure out" which agents may be reasonably

expected to function in the recited manner. Applicants assert that, on the contrary, the skilled artisan is being invited to perform a routine RET screening assay as disclosed in the specification to thereby identify agents that satisfy the requirements of the agent specified in the claim. Applicants note that the skilled artisan is also provided with examples of this assay being used to identify agents with the claimed activities (see, for example, pages 35-36, Table 2a and Table legend).

In addition, applicants respectfully direct the Examiner's attention to item 6 of Dr. Dragic's Third Declaration, attached hereto as **Exhibit A**. Based on her extensive experience with screening for fusion inhibitors using the RET assay, Dr. Dragic asserts that knowledge of the molecular or other structural determinants of the CCR5 receptor is not necessary to identify agents that inhibit CCR5-mediated fusion with HIV-1. In support of this assertion, Dr. Dragic points to the success of various groups in using the RET assay to identify structurally diverse classes of CCR5-mediated fusion inhibitors without knowledge of the molecular determinants on the receptor with which the agents interact. Dr. Dragic notes that, in addition to the β-chemokines and anti-CCR5 antibodies described in the subject application, such inhibitors include non-peptidyl aminopiperidine derivatives described in PCT International Publication No. WO 02/079186, a copy of which was attached as Exhibit 1 to Dr. Dragic's second declaration submitted with applicants' August 27, 2003 Amendment (the "Second Declaration"). Applicants maintain, therefore, that information pertaining to the molecular determinants of the CCR5 receptor that might prove to be suitable targets for a fusion-inhibitory agent is not a requirement for an adequate written description of the claimed invention.

Examiner's Response to Applicant's Previous Arguments

The Examiner noted applicants' traversal in their October 20, 2004 Amendment and their submission that sufficient written support for the claimed invention is clearly present in the specification. However, the Examiner stated that he does not concur with this assessment. The Examiner asserted that perusal of the portions of the specification relied upon fails to provide adequate written support for the large genus of agents claimed. The Examiner also asserted that the only molecules described in any detail are a small number of structurally related compounds, the β-chemokines, which are ligands for the CCR5 receptor. The Examiner stated that perusal of the data pertaining to these compounds illustrates that most of the compounds referenced fail to meet the basic claim limitations.

In this regard, the Examiner stated that the claims require that the agent of interest needs to block fusion of the JR-FL isolate without blocking fusion of the BRU isolate. The Examiner further asserted that a review of the compounds tested indicates that there was considerable variability in the ability of any given compound to block JR-FL-mediated fusion. The Examiner stated that, for example, compounds MIP-1α, MIP-1β, MCP-1, -2, and -3 inhibited fusion 61%, 87%, 1%, 28% and 2%, respectively. The Examiner further stated that fusion inhibitory rates for these same compounds in the context of BRU-mediated fusion were 0%, 7%, 2%, 7% and 1%, respectively. The Examiner asserted that very few of the compounds thus appear to be able to truly block JR-FL-mediated Env fusion events without also inhibiting BRU-mediated Env fusion events. The Examiner also stated that, moreover, the rates of inhibition varied considerably even amongst closely related compounds.

Thus, the Examiner concluded that this example fails to provide sufficient structural information that would put applicants in possession of the claimed genus of agents.

In response, applicants respectfully disagree with the conclusions drawn by the Examiner from the referenced data. Applicants note that the Examiner correctly characterized the activity of MIP-1α, MIP-1β, MCP-1, MCP-2, and MCP-3 in inhibiting fusion of PM-1 cells to the HIV-$1_{JR-FL}$ and HIV-$1_{BRU}$ isolates, respectively. The Examiner omitted to mention that RANTES inhibits fusion of PM-1 cells to HIV-$1_{JR-FL}$ by 92% but showed no inhibition (0%) of fusion to HIV-$1_{BRU}$. Thus, these data reveal that whereas none of RANTES, MIP-1α, MIP-1β, MCP-1, MCP-2, and MCP-3 significantly inhibit fusion of PM-1 cells to HIV-$1_{BRU}$, three of these chemokines, RANTES, MIP-1α, MIP-1β, significantly inhibit fusion to HIV-$1_{JR-FL}$ by 61-92%. Applicants maintain that the fusion-inhibitory activities of these three chemokines satisfy the requirements recited in claim 61. That is, these three chemokines are (a) capable of binding to a CCR5 chemokine receptor on the surface of the CD4+ cell; (b) capable of blocking fusion of HIV-$1_{JR-FL}$ with a PM-1 cell; and (c) not capable of blocking fusion of HIV-$1_{BRU}$ with such PM-1 cell.

Contrary to the Examiner's assertion, applicants maintain that, there is no disclosure in the specification to indicate that there was any variability, much less "considerable variability," in the ability of any given compound to block JR-FL-mediated fusion to PM-1 cells. Applicants also emphatically disagree with the Examiner's conclusion that "very few of the compounds thus appear to be able to truly block JR-FL-mediated Env fusion events without also inhibiting BRU-mediated Env

fusion events." On the contrary, applicants assert that of the agents, i.e., RANTES, MIP-1α and MIP-1β, which significantly inhibited fusion of PM-1 cells to HIV-$1_{JR-FL}$, none significantly inhibited fusion of PM-1 cells to HIV-$1_{BRU}$ (see page 35, Table 2a). Thus, applicants respectfully submit that the Examiner's conclusions set forth above are clearly erroneous, and appear to be based on a misinterpretation of the data disclosed in the specification.

The Examiner stated that applicants further contend that the disclosure provides sufficient means for performing rational drug-screening strategies. The Examiner asserted that the skilled artisan would clearly disagree with this statement. The Examiner further stated that rational drug-screening strategies generally rely upon detailed structural determinations of the target (which are frequently obtained from x-ray crystallographic models) in conjunction with the chemical synthesis of compounds that might be expected to bind in a specific manner to a specific portion of the target. The Examiner further stated that the disclosure fails to provide any detailed structural information pertaining to the molecular determinants of CCR5 that should be targeted. The Examiner invited applicants to identify those domains and the corresponding amino acid regions that should be targeted by a rational drug-screening regimen. The Examiner contended that, absent such a showing, the rejection is clearly tenable.

In response, applicants note that in their October 20, 2004 Amendment (page 9, second paragraph), they described the use of the RET assay to identify agents with the properties specified in claim 61 as a "rational drug-screening strategy." Applicants maintain that the specification provides a rational strategy for

identifying inhibitors of HIV-1 infection based on the RET assay. In this regard, applicants direct the Examiner's attention to Dr. Dragic's First and Second Declarations which emphasize the efficacy of the RET assay in identifying agents that inhibit HIV-1 infection of CD4+ cells without any prior knowledge of the chemical structures of these agents or of their target molecules. See paragraphs 8-17 of the First Declaration and paragraphs 9-11 of the Second Declaration. Applicants also direct the Examiner's attention to the descriptions in the Second Declaration (see paragraphs 6 and 11) of the use of the RET assay by Hoffmann-La Roche AG ("Roche") to identify small nonpeptidyl compounds that inhibit HIV-1 infection. Applicants note that Roche has filed a patent application (PCT International Publication No. WO 02/079186 A2) claiming these compounds *per se* and their use in preventing cell infection by HIV-1.

However, with regard to a rational drug design approach as contemplated by the Examiner, i.e., using detailed structural data and/or models of target molecules to systematically design new drugs, applicants reiterate that such a rational drug-design regimen is not the standard approach to drug development in the pharmaceutical industry. As applicants have discussed hereinabove, this is a new approach to drug development that is still the exception rather than the norm. Thus, applicants maintain that whether or not the specification facilitates rational drug design is not a tenable standard for assessing the adequacy of the written description.

The Examiner also noted applicants' argument that he has ignored the evidence provided by Dr. Dragic in the form of two declarations. The Examiner stated that this evidence was

considered and clearly found to be non-persuasive for the reasons of record. The Examiner further stated that the declaration dated April 8, 2002, asserted that the skilled artisan could use the disclosed FRET assay to identify suitable agents. The Examiner also noted that reference was made to a recently published abstract. The Examiner asserted that this abstract failed to set forth any meaningful structural information pertaining to the compounds that were identified.

The Examiner additionally stated that Dr. Dragic also asserted that page 45 of the specification disclosed a compound that meets the claimed limitations, specifically JM-3100. The Examiner further stated that perusal of the disclosure at pages 45 and 46 clearly demonstrated that JM-3100 did not inhibit JR-FL Env-mediated fusion as required by the claim. The Examiner noted that, in fact, the inventors unambiguously stated that this product binds to CXCR4, not CCR5. The Examiner stated that Dr. Dragic's comments are thus clearly erroneous. The Examiner concluded that the April 8, 2002 declaration failed to provide any evidence that would put applicants in possession of a sufficient number of compounds that would provide a sufficient written description for the claimed genus.

The Examiner also stated that concerning the second declaration, dated August 29, 2003, Dr. Dragic referenced the following in support of her arguments: 1) a post-filing date PCT publication which provided putative compounds that meet the claimed limitations; 2) the earlier referenced abstract was again cited; 3) data from Progenics' in-house experiments involving SCH-C, TAK-779, 7948, and 8260 were provided; and 4) data from a single Mab (e.g., PRO-140) was provided.

The Examiner stated that, first, it should be noted that none of the evidence relied upon directly suggests that applicants were in possession of any of the claimed compounds at the time of filing. The Examiner further stated that Dr. Dragic's declaration clearly fails to state that the inventors had synthesized and identified any of these compounds at the time of filing. The Examiner also stated that, second, much of the data surrounding the inhibitory activity of these compounds is incomplete. The Examiner stated that, for instance, SCH-C inhibitory values were reported for JR-FL isolates but not BRU. The Examiner further stated that a direct and meaningful comparison thus does not appear to have been performed. The Examiner asserted that, third, the fact that others may have identified a limited number of compounds that may meet the claim limitations does not put them in applicants' possession at the time of filing. The Examiner contended that the crux of the rejection is not whether or not one skilled in the art could use the disclosed FRET assay to identify putative antiviral agents, but whether or not applicants had already used said assay to identify a reasonable number of compounds that would justify the breadth of the claim language directed toward any agent. The Examiner asserted that the skilled artisan, upon considering the teachings of the disclosure, would reasonably conclude that applicants were clearly not in possession of the claimed compounds at the time of filing.

In response, applicants respectfully submit that the Examiner has clearly taken Dr. Dragic's statements in her two prior declarations out of their proper contexts. First, applicants note that in her First Declaration, Dr. Dragic explicitly stated (see paragraph 5) that she was addressing a rejection based on an alleged lack of enablement. In this regard, applicants note

that in the Office Action issued October 2, 2001 in response to which Dr. Dragic's First Declaration was filed, the Examiner rejected the pending claims under 35 U.S.C. 112, first paragraph, as allegedly not enabled. Applicants also note that this Office Action contained no rejection based on any alleged inadequacy of the written description. Thus, as Dr. Dragic notes in item 7 of her Third Declaration attached hereto (**Exhibit A**), she sought in her First Declaration to identify evidence that the disclosure was enabling, for which the provision of structural information pertaining to the identified compounds would have been irrelevant.

Second, the Examiner cited Dr. Dragic's reference to JM-3100 as an example of a compound that satisfies the elements of the claims, and asserted that this reference to JM-3100 is "clearly erroneous." However, as Dr. Dragic notes in item 8 of her Third Declaration, independent claim 61 then pending, with reference to which she cited JM-3100, read:

> A method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with a nonpeptidyl agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 or an HIV-1 infected cell to the CD4+ cell is inhibited, so as to thereby inhibit HIV-1 infection of the CD4+ cell, provided that the nonpeptidyl agent is not a bicyclam or a derivative thereof.

As Dr. Dragic explains in item 8 of the Third Declaration, JM-3100 is a valid example of an agent that exhibits the activities of the agent recited in claim 61, as pending at the time the First Declaration was submitted. Dr. Dragic also points out that she did not suggest that JM-3100 inhibits JR-FL Env-mediated fusion as required by now pending claim 61. On the contrary, Dr. Dragic explicitly stated (see paragraph 13 of the

First Declaration) that "JM-3100 specifically and potently inhibits fusion mediated by gp120/gp41 from the $gp120_{LAI}$ [$gp120_{BRU}$] strain, but not from the $gp120_{JR-FL}$ strain (p. 46, lines 7-10)." As Dr. Dragic asserts in item 8 of the Third Declaration, this was and is an accurate statement regarding the fusion-inhibitory properties of JM-3100.

Applicants assert, further, that whereas some of Dr. Dragic's statements no longer pertain to claim 61 as now pending, these statements were all accurate in the context in which they were made. Accordingly, applicants maintain that the Examiner's characterization of Dr. Dragic's statements as "clearly erroneous" is without merit. Further, applicants maintain that the Examiner's statement that Dr. Dragic's First Declaration failed to provide evidence of a sufficient written description for the claimed genus overlooks the fact that the First Declaration addresses an alleged lack of enablement rejection.

Regarding the Examiner's comments on Dr. Dragic's Second Declaration, applicants note the Second Declaration, similar to the First Declaration, addressed an enablement rejection (in this case, the enablement rejection issued in the February 27, 2003 Final Office Action). Thus, in response to the Examiner's statements that the evidence relied upon by Dr. Dragic does not directly suggest that applicants were in possession of any of the claimed compounds at the time of filing, or that the declaration fails to state that the inventors had synthesized and identified any of these compounds at the time of filing, applicants respectfully point out that these were not the issues being addressed in either the First or Second Declaration. In this regard, applicants emphasize that the Examiner did not issue any "written description" rejection of the claim(s) in this application until in the April 20, 2004 Office Action, and thus

neither of Dr. Dragic's First or Second Declarations addressed a written description rejection.

Accordingly, applicants respectfully point out to the Examiner that the post-filing date publications cited by Dr. Dragic had not been used to show what was known at the time of filing. Rather, Dr. Dragic properly cited these publications as evidence that the disclosures in the specification as filed are sufficient to enable a person skilled in the art to practice without undue experimentation the invention being claimed at that time, i.e., to demonstrate that the disclosure was enabling as of the filing date. Applicants note that the Examiner appears to have been persuaded by this evidence since rejections based on an alleged lack of enablement have not been maintained in the February 9, 2005 Final Office Action.

Applicants note that some of the factors upon which the Examiner grounded the previous "enablement" rejections (for example, failure to provide structural guidance pertaining to suitable compounds; and failure to provide any guidance pertaining to the molecular determinants of the CCR5 receptor) have been repeated as the bases of the instant "written description" rejection. Applicants note also that Dr. Dragic addressed certain of these issues in her First and Second Declarations. Though Dr. Dragic's expert statements were made in relation to different claims pending at the time, applicants contend that one of the central points of her comments, i.e., that the RET assay can be used to readily identify agents with specified fusion inhibitory properties without any prior knowledge of the structure of these agents (see paragraphs 14-17 of the First Declaration; and paragraph 12 of the Second Declaration), remains valid with regard to the now pending claim.

Thus, notwithstanding that Dr. Dragic addresses enablement rejections in her First and Second Declarations, applicants contend that certain of her statements therein are pertinent to the instant written description rejection. In addition, Dr. Dragic directly addresses this written description rejection in her Third Declaration attached hereto (**Exhibit A**). Applicants remind the Examiner that he is required to consider and give weight to these expert declarations, and if the statements therein are rejected, specific reasons have to be provided by the Examiner for rejecting them. See M.P.E.P. §2164.05:

> Applicant may submit factual affidavits under 37 CFR 1.132 or cite references to show what one skilled in the art knew at the time of filing the application. A declaration or affidavit is, itself, evidence that must be considered. (emphasis in original)

See also *In re Alton,* 37 U.S.P.Q.2d 1578, 1582 (Fed. Cir. 1996):

> [T]he examiner's final rejection and Answer contained two errors: ... (2) the summary dismissal of the declaration, without an adequate explanation of why the declaration failed to rebut the Board's *prima facie* case of inadequate written description.

Applicants also disagree with the Examiner's characterization of the crux of the instant rejection as being whether or not applicants had already used the RET assay to identify a reasonable number of compounds that would justify the breadth of the claim language directed toward any agent, or whether the skilled artisan, upon considering the teachings of the disclosure, would reasonably conclude that applicants were in possession of the "claimed compounds" at the time of filing. In this regard, applicants remind the Examiner that the pending claim is not directed to an agent or a compound. Instead, the claim is directed to a method of inhibiting infection of a CD4+

cell by a macrophage-tropic HIV-1, comprising contacting the CD4+ cell with an agent having defined fusion-inhibitory properties, which agent is identifiable by the RET assay as disclosed in the specification. Moreover, applicants note that the specification discloses that the agent may be an oligopeptide, a polypeptide, an antibody or a portion thereof, or a nonpeptidyl agent (see, for example, page 14, lines 13-22; page 20, lines 22-27; page 45, lines 33-35), and provides three examples of chemokines that exhibit the properties of the agent recited in the claim (see, *inter alia*, page 26, lines 8-18; page 34, lines 33-37; and page 35, Table 2a).

In view of the foregoing remarks and arguments, applicants maintain that the specification as filed satisfies the written description requirements of 35 U.S.C. §112, first paragraph, with regard to pending claim 61.

**Conclusion**

The Examiner's focus of the instant "written description" rejection is predicated on the basis that applicants are claiming a broad genus of agents that inhibit HIV-1 infection whereas too few examples have been provided in the specification to support such a broad claim. Applicants reiterate that the pending claim is directed, not to a broad genus of agents, but to a method of inhibiting infection of a CD4+ cell by a macrophage-tropic HIV-1 isolate. Applicants maintain that their remarks set forth hereinabove, and the expert opinions presented by Dr. Dragic in her Third Declaration attached hereto (**Exhibit A**), obviate all the grounds of the "written description" rejection issued by the Examiner. Based on these remarks and supporting expert opinions, applicants respectfully request that

the Examiner reconsider and withdraw the rejection of claim 61 set forth in the February 9, 2005 Final Office Action, and earnestly solicit allowance of this pending claim, as amended.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

A fee of SIXTY DOLLARS ($60.00) is required for a one-month extension of time for responding to the February 9, 2005 Final Office Action, and a check for this amount is enclosed. No other fee is deemed necessary in filing this response. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Attorney for Applicants
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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

6/8/05

John P. White Date
Reg. No. 28,678

Dkt. 50875-F-PCT-US/JPW/AJD

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants: Graham P. Allaway et al.

Serial No.: 09/460,216 Examiner: Jeffrey S. Parkin

Filed: December 13, 1999 Group Art Unit: 1648

For: METHODS FOR PREVENTING HIV-1 INFECTION OF CD4+ CELLS

1185 Avenue of the Americas
New York, New York 10036

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

**THIRD DECLARATION UNDER 37 C.F.R. §1.132 OF TATJANA DRAGIC**

I, Tatjana Dragic, Ph.D, hereby declare that:

1. I am the Tatjana Dragic who previously provided the "Declaration Under 37 C.F.R. §1.132 Of Tatjana Dragic" dated March 31, 2002 ("First Declaration") and the "Second Declaration Under 37 C.F.R. §1.132 Of Tatjana Dragic" dated April 26, 2003 ("Second Declaration"), in connection with the above-identified application. The contents of my prior Declarations are hereby incorporated by reference into this Third Declaration.

2. This Third Declaration addresses the "written description" rejection of pending claim 61 of the subject application as set forth in the February 9, 2005 Final Office Action, and the Examiner's comments on pages 6-7 of the Office Action regarding my First and Second Declarations.

**A. The Invention**

3. I understand the invention claimed in the above-identified application to be a method of inhibiting infection of a CD4+

cell by a macrophage-tropic HIV-1. Specifically, I understand the invention to be a method which involves contacting the CD4+ cell with an agent which (a) is capable of binding to a CCR5 chemokine receptor on the surface of the CD4+ cell and blocking fusion of HIV-$1_{JR-FL}$ with a PM-1 cell, but (b) is not capable of blocking fusion of HIV-$1_{BRU}$ with a PM-1 cell.

**B. Written Description**

4. I understand that to satisfy the written description requirement, the patent application must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Further, I understand that factors to be considered in determining whether there is sufficient evidence that the inventor had possession of the invention include the level of skill and knowledge in the art, and the disclosure sufficiently detailing, relevant identifying characteristics of the claimed invention.

5. As stated in item 7 of my First Declaration, the level of skill and knowledge in the art is very high, and based on the present patent application, a person skilled in the art would readily conclude that the inventors had possession of the claimed invention. This assertion is predicated on the fact that the application teaches inhibition of fusion of a PM-1 cell with HIV-$1_{JR-FL}$ by agents which do not inhibit fusion of a PM-1 cell with HIV-$1_{BRU}$. Examples of such agents are RANTES, MIP-1α and MIP-1β (see Figure 1 and page 7, lines 3-30; page 35, Table 2a) and anti-CCR5 antibodies (see page 45, lines 33-35). Thus, the skilled person is provided agents which can be used to inhibit infection of a CD4+ cell by a macrophage-tropic HIV-1 strain. This assertion is further based on the fact

that the application discloses identifying characteristics of the agent utilized in the claimed method, namely, its specificity in binding to the CCR5 receptor (page 13, lines 4-5; 19-20 and 33-34; page 40, lines 9-11; and page 41, lines 4-8); ability to inhibit fusion of a PM-1 target cell to HIV-$1_{JR-FL}$; and inability to inhibit fusion of a PM-1 target cell to HIV-$1_{BRU}$ (page 35, Table 2a). This assertion is also based on the fact that the application discloses a function of the agent, namely, its ability to bind to a CCR5 receptor on the surface of a target cell. In this regard, I note that there is a clear correlation between the function and the identifying characteristics of the agent. Finally, this assertion is based on the fact that the application provides a resonance energy transfer (RET) assay (see pages 35-36, legend to Table 2) which one skilled in the art could, as of April 2, 1996, readily use to identify additional agents that exhibit the fusion-inhibitory activities specified in the pending claims.

6. On page 4 of the Office Action, the Examiner stated that the disclosure in the application fails to provide any guidance pertaining to the molecular determinants of the CCR5 receptor that might prove to be suitable targets (i.e., epitopes, active domains, etc.) for a putative fusion inhibitor. In response, based on my extensive experience with screening for fusion inhibitors using the RET assay, knowledge of the molecular or other structural determinants of the CCR5 receptor is not necessary to identify agents that inhibit CCR5-mediated fusion with HIV-1. This view is supported by the success of various groups in using the RET assay to identify structurally diverse classes of CCR5-mediated fusion inhibitors without knowledge of the molecular determinants on the receptor with which the agents interact. In addition to the β-chemokines and

anti-CCR5 antibodies described in the subject patent application, such inhibitors include non-peptidyl aminopiperidine derivatives (see, e.g., PCT International Publication No. WO 02/079186).

**C. The Examiner's Comments Concerning My Prior Declarations**

7. On page 6 of the Office Action, the Examiner stated that a published abstract cited in my First Declaration failed to set forth any meaningful structural information pertaining to the fusion inhibitors that were identified. In response, I note that this First Declaration was filed in response to an "enablement" rejection under 35 U.S.C. 112, first paragraph. There I explained that structural information pertaining to identified fusion inhibitors was not relevant to the presentation of evidence supporting the enablement of the subject application for the then claimed invention.

8. The Examiner further stated that I also asserted that page 45 of the specification discloses a compound, specifically JM-3100, that meets the claimed limitations. The Examiner additionally stated that perusal of the disclosure at pages 45 and 46 clearly demonstrates that JM-3100 did not inhibit JR-FL Env-mediated fusion as required by the claim, since the inventors unambiguously stated that JM-3100 binds to CXCR4, not CCR5. The Examiner concluded that my comments are thus "clearly erroneous," and that my First Declaration failed to provide any evidence that would put applicants in possession of a sufficient number of compounds to constitute a sufficient written description for the claimed invention.

In response, I note that then-pending independent claim 61, with reference to which I cited JM-3100, read:

> A method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with a nonpeptidyl agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 or an HIV-1 infected cell to the CD4+ cell is inhibited, so as to thereby inhibit HIV-1 infection of the CD4+ cell, provided that the nonpeptidyl agent is not a bicyclam or a derivative thereof.

I maintain that JM-3100 is a valid example of an agent that exhibits the activities recited in then-pending claim 61. Further, I did not suggest that JM-3100 inhibits JR-FL Env-mediated fusion as required by now-pending claim 61. On the contrary, I explicitly stated (see page 5, paragraph 13 of my First Declaration) that "JM-3100 specifically and potently inhibits fusion mediated by gp120/gp41 from the $gp120_{LAI}$ [$gp120_{BRU}$] strain, but not from the $gp120_{JR-FL}$ strain (p. 46, lines 7-10)." This was and is an accurate statement regarding the fusion-inhibitory properties of JM-3100, supported by the specification at page 46, lines 1-12. The Examiner's characterization of the referenced statements in my First Declaration as "clearly erroneous" is thus itself in error.

9. On pages 6-7 of the Office Action, the Examiner enumerated the evidence I relied upon in my Second Declaration, and asserted that none of this evidence directly suggests that applicants were in possession of any of the claimed compounds at the time of filing.

In response, I reiterate that my Second Declaration related to my opinion that the specification, as filed, enabled the then-claimed invention. I address the issue of the sufficiency of the written description for the first time in this Third Declaration.

I hereby declare that the statements made herein of my own knowledge are true and that all statements made on information and

belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 5/30/05

T. Dragic

Tatjana Dragic, Ph.D.